REMARKS

Claims 1-39 constitute the pending claims in the present application. Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the outstanding Office Action.

1. Applicants acknowledge that Applicants' selection of Group 1, i.e., claims 1-40 drawn to a pharmaceutical preparation comprising a nefazodonoid and a fluoxetinoid serotonin reuptake inhibitor (SRI), and a method for its preparation, has been made final. Applicants are unclear as to why the Office Action proceeded to state that claims "4, 10-13, 41-46, are withdrawn from consideration as being drawn to non-elected inventions." While Applicants acknowledge that claims 41-46 are non-elected claims, Group 1, set forth in the original Restriction Requirement, includes claims 1-40. As such, Applicants' election of Group I, which the Office Action has made final, necessarily contains claims 4 and 10-13. Applicants request examination of these claims. As to claims 41-46, Applicants have herein cancelled these non-elected claims. Applicants assert that this cancellation is entered solely to expedite prosecution, and Applicants reserve the right to pursue claims of the same or similar scope at a later date.

2. Applicants acknowledge that the USPTO has received and reviewed three IDSs Applicants filed, respectively, September 11, 2002, January 21, 2003, and July 21, 2003 (Paper Nos. 5-7). Applicants note that they are filing a supplemental IDS along with this response.

3. The disclosure is objected to because claims 6 and 40 are allegedly substantial duplicates, and because the intended use language in claim 40 is allegedly does not confer patentable weight to a composition claim such as claim 40. Applicants have herein cancelled claim 40. Applicants respectfully request reconsideration and removal of the rejection.

4. Claims 7 and 39 are rejected under U.S.C. 112, 2nd paragraph, for being indefinite. Applicants respectfully traverse this rejection to the extent it is maintained over the claims as amended.

At issue in claim 7 is the recitation of the phrases "preferably H or Me" and "preferably O" in the definitions R_1 and Y respectively. Applicants have herein amended the claim by

remove these phrases. Applicants assert that the amendment in no way narrows the scope of the claim because these phrases recite exemplary embodiments already covered within R_1 and Y.

At issue in claim 39 is the manner with which the method of preparing a pharmaceutical composition comprising a nefazodonoid and a fluoxetinoid is described. Specifically, the Office Action stated that Applicants have allegedly failed to define the invention properly with respect to the method for preparing the pharmaceutical preparation, and that, by definition, a composition is a product of combining various ingredients. The Office Action further stated that an unobvious or novel element in the preparation is absent.

At the outset, Applicants point out that 35 U.S.C. 112, 2nd paragraph, requires neither novelty nor unobviousness. Nonetheless, solely to expedite prosecution, Applicants have herein amended the claim to direct it to a method of preparing a pharmaceutical composition comprising a nefazodonoid and a fluoxetinoid which is suitable for simultaneous administration to a patient. Applicants assert that the amended claim is clear and definite. Applicants further assert that the amendment in no way narrows the scope of the claim because the amendment merely elucidates what was already covered by the original claim.

In view of the amendments presented above for claims 7 and 39, Applicants respectfully request reconsideration and removal of the rejections of these claims.

5. Claims 1-3, 5, 7, 14-18 and 25-31 are rejected under 35 U.S.C. 112, first paragraph, for allegedly lacking clear written description, and for not setting forth the best mode contemplated by Applicants to carry out the invention. Applicants respectfully traverse the rejection.

One issue the Office Action raised is the fact that the specification only discloses a nefazodone and fluoxetine combination, whereas the claims are directed to combinations of a nefazodonoid and a serotonin reuptake inhibitor (SRI). Applicants point out, however, that the specification teaches a variety of known nefazodonoids, including nefazodone, hydroxynefazodone, and oxonefazodone, and a variety of known SRIs, including venlafaxine, sertralin, citalopram, fluvoxamine, ericlamine, paroxetine, femoxetine, ifoxetine, cyanodothiepin, and litoxetine, as being suitable for use in the claimed methods. (See, e.g., *Exemplary Embodiments* section of the specification starting on page 16, last paragraph, to page

26, first paragraph.) In addition, the specification teaches the principle behind simultaneously administering a nefazodonoid and an SRI, such that one of skill in the art would anticipate that the same benefit would be achieved with SRIs other than fluoxetine, and nefazodonoids other than nefazodone itself. (See specification on page 6, 2nd full paragraph.) Since one embodiment of the invention is to reduce side-effects of high-dose nefazodone treatment, yet still achieve the same desired therapeutic effect resulting from 5-HT receptor antagonism and serotonin reuptake inhibition, one of ordinary skill in the art would realize that other nefazodonoids and SRIs can be utilized without departing from the subject matter of the present invention.

The Office Action also alleged that the specification is deficient because there is "no disclosure concerning any 5-HT receptor mediated disorder." Applicants direct the Examiner's attention to page 31, 2nd full paragraph, and page 32, 2nd and 3rd paragraphs, where Applicants explicitly disclose various types of 5-HT receptor-mediated disorders, and cite to scientific and patent references containing additional discussions on these 5-HT receptor-mediated disorders. Thus, contrary to the Office Action's assertions, the specification provides sufficient guidance regarding therapeutic application of simultaneous administration of a nefazodonoid with a SRI.

The Office Action alleged that claim 26 does not find support in the specification because there is no showing that Applicants had possession of the claimed invention other than what was well known in the prior art. Applicants respectfully disagree with the Office Action's conclusions.

Applicants point out that the requirement of 35 U.S.C. 112, 1st paragraph, is met so long as the patent specification describes the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. (See MPEP 2163 quoting Vas-Cath, Inc. v. Mahurkar, 935 F.2d at 1563, 19 USPQ2d at 1116.) Claim 26 is directed to a method for treating a 5-HT receptor-mediated disorder in an animal, comprising co-administering to the animal an amount of a nefazodonoid sufficient to inhibit a 5-HT_2 receptor activity to a therapeutically effective extent, and an amount of a serotonin reuptake inhibitor (SRI) sufficient to inhibit serotonin reuptake to a therapeutically effective extent, wherein the nefazodonoid is administered at a dosage below the necessary dosage to inhibit serotonin reuptake to a therapeutically effective extent in the absence of the SRI. Applicants

assert that the particularity with which the claim identifies the etiology of the disease to be treated, the agents to be administered, and the specific relative dosages of these agents to be administered, would reasonably lead one of skill in the art to conclude that Applicants had possession of the full scope of the claimed invention at the time of filing.

The Office Action further stated that the present level of skill in the art of psychiatry would reasonably require a more detailed written description directed to the means of carrying out treatment of 5-HT receptor-mediated disorders and disclosures as to what disorders are contemplated. Applicants address this issue in detail in point 6 below.

6. Claims 26-34 are rejected under 35 U.S.C. 112, 1st paragraph, for containing subject matter which was not described in the specification in such a way as to enable a skilled artisan to make or use the invention. Applicants traverse the rejections.

One issue the Office Action raised is the fact that the specification only discloses a nefazodone and fluoxetine combination, whereas the claims are directed to combinations of a nefazodonoid and a serotonin reuptake inhibitor (SRI). Applicants direct the Examiner's attention to point 5 above where Applicants have addressed this issue.

Another issue raised by the Office Action is that the specification is deficient because there is "no disclosure concerning any 5-HT receptor mediated disorder." Applicants direct the Examiner's attention to point 5 above where Applicants have addressed this issue.

The Office Action further listed each of the *In re Wands* factors and alleged that claims 26-34 are rejected for lack of enablement. Applicants respectfully disagree with the Office Action's conclusions.

At issue is whether a skilled artisan, having read the instant application, would have known how to make and use what is claimed in claims 26-34. Claim 26 is the independent claim in the rejected claim set. Claim 26 is directed to a method for treating a 5-HT receptor-mediated disorder in an animal, comprising co-administering to the animal an amount of a nefazodonoid sufficient to inhibit a 5-HT_2 receptor activity to a therapeutically effective extent, and an amount of a serotonin reuptake inhibitor (SRI) sufficient to inhibit serotonin reuptake to a therapeutically effective extent, wherein the nefazodonoid is administered at a dosage below the necessary

dosage to inhibit serotonin reuptake to a therapeutically effective extent in the absence of the SRI. Thus, to make and use the claimed inventions, a skilled artisan must know at least one nefazodonoid and at least one SRI, and be able to simultaneously administer them in appropriate dosages to an animal with a 5-HT receptor-mediated disorder, or to combine them in a pharmaceutical composition in a manner suitable for administration.

As the Office Action states, the skill of those in the art is high, i.e., generally that of a Ph.D. or an M.D. Applicants assert that such a skilled artisan has the knowledge, training and researching capabilities to identify what are 5-HT (serotonin) receptor-mediated disorders, particularly in light of the conditions identified in the present application, e.g., at page 31, 2nd full paragraph, and page 32, 2nd and 3rd paragraphs. Moreover, one need only enter the terms "serotonin receptor" and "disorder" in MEDLINE to identify a multitude of references about the subject that had been published prior to the filing date of the present application.

The skilled artisan would also need to know what a nefazodonoid and an SRI are. Applicants submit that it is well within the knowledge, training and researching capabilities of a Ph.D. or an M.D. to be able to identify these compounds either by looking at structural similarities, or by reviewing published literature accounts of SRIs and of analogs of nefazodone. Even if such knowledge weren't widely available, Applicants submit that the specification alone provides many examples of SRIs and of nefazodone analogs that would be sufficient to enable one of skill in the art to select from among a substantial number of suitable compounds for carrying out the claimed methods. (See specification on pages 16-26.)

Having identified an animal or patient with any of these disorders, and having identified a nefazodonoid and an SRI (e.g., fluoxetine, or a fluoxetinoid), the skilled artisan can then simultaneously administer the drugs to treat the disorder. The specification provides adequate support for claim 26. For example, the specification on page 26, first full paragraph, provides guidance as to the magnitude of prophylactic or therapeutic doses of an SRI and a nefazodonoid to be administered to a patient. Moreover, on pages 31-32, the specification provides guidance for dosages of a conjoint administration of SRI and a nefazodonoid. While the exact amount of drug to administer will obviously depend on the active agent, the disorder, and the patient, Applicants submit that it does not take a Ph.D. to follow the guidance provided in the

specification to adjust the dosage to treat the patient. For instance, in the case of depression a skilled artisan can evaluate the efficacy of the simultaneous administration of a nefazodonoid with an SRI using any one of several clinical measurement scales including: Beck Depression Inventory (BDI)(Beck AT, Ward CH, Mendelson M, et al. An inventory for measuring depression. Arch Gen Psychiatry. 1961; 4:561–571); Clinical Global Impressions-Severity of Illness Scale (CGI-S)(Guy W. Early Clinical Drug Evaluation (ECDEU) Assessment Manual. Rockville: National Institute Mental Health; 1976); and Udvalg für Kliniske Undersogelser side effect rating scale (Lingjaerd O, Ahlfors UG, Bech P, et al. The UKU side effect rating scale. Acta Psychiatr Scand. 1987; 76(suppl 334):1–100).

The Office Action gives undue attention to the fact that there might be much experimentation involved in figuring out the exact dosage of a nefazodonoid and an SRI to treat a particular 5-HT receptor-mediated disorder. The Office Action stated that there would be undue experimentation absent a reasonable a priori expectation of success for using a particular chemotherapeutic combination to treat any particular 5-HT disorder.

As a threshold matter, an "a priori reasonable expectation of success" is not a requirement that is found in either the MPEP or In re Wands to support a finding of undue experimentation. Applicants further assert that the Office Action incorrectly applied the legal standard for quantity of experimentation. The proper inquiry is whether one of skill in the art who carries out the claimed method will achieve success without undue experimentation, not whether that person would be convinced from the start that success will result. Implicit in any treatment of a disease is the recognition that different patients may have different tolerances and reactions to the same drug. A psychiatrist, for instance, would need to adjust the dosage or formulation of a certain CNS drug to optimize a treatment plan for a given patient. But such optimization does not constitute undue experimentation, because the optimization is a routine aspect of tailoring the general treatment plan to a specific patient. (See, e.g., Exhibit A: FDA approved label instructions for Prozac (fluoxetine).)

The MPEP recognizes that "a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." (See MPEP 2164.06

quoting In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).) What Applicants have presently claimed is a generalized treatment plan comprising administering a nefazodonoid and an SRI to a patient with a 5-HT receptor-mediated disorder. The particulars of determining how much of each to give to any given patient is an optimization exercise that is routine in the medical arts, and does not constitute undue experimentation. The specification provides guidance on classes of compounds which can be identified as nefazodonoids or SRIs; provides specific examples of nefazodonoids and SRIs; gives guidance as to how much of a nefazodonoid to administer vis-à-vis the SRI; and provides general dosage regimens for the co-administration of a nefazodonoid and an SRI. For these reasons, Applicants assert that a skilled artisan can make and use the claimed invention without undue experimentation.

7. Claims 1-3, 5-9 and 14-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fava M., J. Clin. Psychiatry, in view of the web site Mhi Ask the Expert-SSRI and Nefazodone. Applicants point out that they have cancelled claim 40. Applicants traverse the rejection of the remaining claims.

Applicants assert that the cited references, alone or in combination, do not teach or suggest all the elements of the present claims. Both references teach administering the nefazodone separately from the SSRI disclosed therein. Thus, neither reference teaches or suggests formulating nefazodone with an SRI in a pharmaceutical preparation, e.g., a single dosage form, as claimed in claims 1, 19, or 25, and claims dependent thereon.

Applicants also assert that the method claims in the rejected set are not rendered obvious by the cited references. Claim 26 is directed to method for treating a 5-HT receptor-mediated disorder in an animal, comprising co-administering to the animal an amount of a nefazodonoid sufficient to inhibit a 5-HT_2 receptor activity to a therapeutically effective extent, and an amount of a serotonin reuptake inhibitor (SRI) sufficient to inhibit serotonin reuptake to a therapeutically effective extent, wherein the nefazodonoid is administered at a dosage below the necessary dosage to inhibit serotonin reuptake to a therapeutically effective extent in the absence of the SRI. There is no teaching or suggestion, in either of the references, or in the combination thereof, that the dosage of nefazodonoid administered be sufficient to inhibit a 5-HT_2 receptor activity to a therapeutically effective extent, and that the amount of the SRI be sufficient to

inhibit serotonin reuptake to a therapeutically effective extent, yet that the nefazodonoid is administered at a dosage below the necessary dosage to inhibit serotonin reuptake to a therapeutically effective extent in the absence of the SRI. Accordingly, neither reference teaches or suggests all the limitations of claim 26, and claims dependent thereon.

With respect to claims 35, 37, and 38, Applicants point out that Fava does not teach or suggest the dosage of nefazodone recited in these claims. The Fava reference discloses a nefazodone dosage of 100 mg or 200 mg administered twice daily. This dosage is much higher than the claimed range which is less than 100 mg or less per day, or more preferably less than 50 mg per day. This difference in dosage highlights the unobviousness of these claims because the claimed therapeutic effect is achieved with much lower dosages of nefazodone than were ordinarily used or were expected to be effective.

Even though the Fava reference mentions augmentation of an SRI with nefazodone, it actually teaches away from using such a combination on grounds that it can cause what is known as a serotonin syndrome. "A prima facie case of obviousness can be rebutted if the applicant...can show that the art in any material respect `taught away' from the claimed invention...A reference may be said to teach away when a person of ordinary skill, upon reading the reference...would be led in a direction divergent from the path that was taken by the applicant." (See MPEP 1504.03 quoting In re Haruna, 249 F.3d 1327, 58USPQ2d 1517 (Fed. Cir. 2001.) Applicants assert that one of ordinary skill in the art, having read Fava, would be less inclined to co-administer a nefazodonoid with an SRI in view of the disclosed serotonin syndrome risk. Similarly, the Mhi reference also cautions against the simultaneous administration of nefazodone and SSRI, citing the serotonin syndrome risk. As such, both cited references do not support a prima facie case of obviousness, because both teach away from the simultaneous administration of nefazodone and SSRI.

Furthermore, the Mhi reference on its face does more to undermine the simultaneous administration of a nefazodonoid and an SRI than it does to support the obviousness of such an administration. That the reference lacks a reasonably enabling disclosure is evidenced plainly in its acknowledgement that to the best knowledge of the responder that "there are no published studies on the combination of an SSRI with nefazodone." The reference only offers that a

nefazodone/SRI combination is one of several combinations that one might try. However, the reference does not appear to endorse this regimen because the advice-giver later states "frankly, though, I've had better results combining SSRIs with dopaminergic agents, such as methylphenidate." Applicants assert that one of ordinary skill in the art reading this disclosure, would be dissuaded from trying the presently claimed subject matter, and certainly would have no reason to expect the particular advantages identified by Applicants.

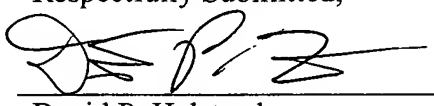
The Supplemental IDS Applicants are filing with this response contains several email communications regarding combination of nefazodone with an SRI. The authors of these published emails note that not only has the combination not been tested extensively, but they also caution against the claimed combination because of well-documented incidences of serotonin syndrome. One practitioner goes as far as to point out that when he adds nefazodone to SSRIs, his patients "get sedated and are most unhappy." Applicants submit that these observations, too, teach away from the presently claimed subject matter, further underscoring the non-obviousness of the claimed subject matter.

In light of the arguments presented above, Applicants respectfully request removal of the rejection of claims 1, 19, 25, 26, 35, 39, and claims dependent thereon.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants submit that the pending claims are in condition for allowance. Early and favorable reconsideration is respectfully solicited. The Examiner may address any questions raised by this submission to the undersigned at 617-951-7000. Should an extension of time be required, Applicants hereby petition for same and request that the extension fee and any other fee required for timely consideration of this submission be charged to **Deposit Account No. 18-1945.**

Respectfully Submitted,



David P. Halstead
Reg. No. 44,735

Date: January 13, 2004

Customer No: 28120
Docketing Specialist
Ropes & Gray LLP
One International Place
Boston, MA 02110
Phone: 617-951-7000
Fax: 617-951-7050